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ORIGINAL CONTRIBUTION

Maternal breastfeeding and attention-deficit/hyperactivity disorder in children: a meta-analysis

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Abstract
Previous studies have suggested environmental factors may contribute to the risk of attention-deficit/hyperactivity disorder (ADHD). The current meta-analysis examined (1) the difference in the duration of maternal breastfeeding between children with and without ADHD, and (2) the association between maternal breastfeeding and ADHD in children. The data of individual studies were synthesized with a random-effects model. Eleven articles were included in this meta-analysis. Children with ADHD had significantly less breastfeeding duration than controls (Hedges' $g = -0.36$, 95% confidence intervals (CIs) = − 0.61 to − 0.11, $p = 0.005$; difference in means: − 2.44 months, 95% CIs = − 3.17 to − 1.71, $p < 0.001$). In addition, the rates of non-exclusive breastfeeding in children with ADHD is significantly higher in "under 3 months" (odds ratio (OR) = 1.90, 95% CIs = 1.45 to 2.48, $p < 0.001$) but lower in "6 to 12 months" (OR = 0.69, 95% CIs = 0.49 to 0.98, $p = 0.039$) and "over 12 months" (OR = 0.58, 95% CIs = 0.35 to 0.97, $p = 0.038$) than controls. Children with ADHD received significantly higher rate of exclusive breastfeeding duration "under 3 months" (OR = 1.51, 95% CIs = 1.20 to 1.89, $p < 0.001$) but lower in "over 3 months" (OR = 0.52, 95% CIs = 0.29 to 0.95, $p = 0.033$) than controls. Furthermore, an association was found between non-breastfeeding and ADHD children (adjusted OR = 3.71, 95% CI = 1.94 to 7.11, $p < 0.001$). Our results suggest maternal breastfeeding is associated with a lower risk of ADHD in children. Future longitudinal research is required to confirm/refute these findings and to explore possible mechanisms underlying this association.

Keywords Attention-deficit/hyperactivity disorder · Breastfeeding · Meta-analysis · Nutrition · Risk

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
BF	Breastfeeding
CI	Confidence interval
CPRS	Conners' Parent Rating Scale
CTRF	Conners' teacher rating form
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
DSM-IV	Diagnostic and statistical manual of mental disorders, fourth edition
ES	Effect size
ICD-10	International statistical classification of diseases and related health problems 10th revision
MA	Meta-analysis
MOOSE	Meta-analysis of observational studies in epidemiology
n/a	Not available
NOS	Newcastle–Ottawa scale
OR	Odds ratio
PUFAs	Polyunsaturated fatty acids

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder whose onset typically occurs during childhood [1, 2]. It is characterized by symptoms including inattentiveness, hyperactivity and impulsiveness, variably presenting across different individuals. It was estimated that ADHD may affect up to 7.2% of children based on parents' report in the US [3]. Children with ADHD can often experience difficulties in areas such as learning (i.e., in the area of academic achievement), behavioral, and emotional problems [4]. Its potential burden on the individual and family is considerable and financial costs can also be significant [5]. Therefore, the identification of potentially modifiable risk factors that could ultimately aid in the prevention of this neurodevelopmental disorder is important.

Whilst it is clear that ADHD has a genetic component, recently, there is an increasing evidence suggesting that environmentally risk factors, which are potentially modifiable, may contribute to the risk of ADHD [6, 7]. To date, numerous environmental factors have been considered to increase the risk of ADHD, including maternal bleeding, tobacco smoking, social and family circumstances, illicit drug use, air pollution, pesticides, and nutritional deficiency [8, 9].

Previous studies have explored the possible influences of breastfeeding on the underlying pathophysiology of ADHD [10, 11]. For example, it was thought that, through external stimulation during breastfeeding, the increasing oxytocin levels may also be protective against the development of ADHD [10, 12]. Additionally, the lack of specific neurotrophic factors in formula milk compared to human milk may lead to a negative impact on children's brain development [11]. In addition, one sibling-controlled study provided evidence that the promotion of breastfeeding might modify the process of ADHD via investigation of comparison of the presence of breastfeeding in children diagnosed with ADHD with their sibling controls across different ages [13]. However, the results of previous studies considering breastfeeding and ADHD in children are controversial thus far. Some studies have reported a reduced rate or duration of breastfeeding in children with ADHD than in controls [13–16], whereas other studies have found a more complicated pattern of association between ADHD and breastfeeding [17, 18]. For example, in the study by Field [17], the breastfeeding reduced ADHD risk only in the absence of parental psychopathology but was a risk for ADHD in situation of maternal history of psychopathology. Furthermore, when the breastfeeding duration was under 3 months, the rate of breastfeeding did not have any significant difference between children with ADHD and controls in the study by Ptacek et al. [18] but was more prevalent in ADHD than in controls [16]; however, when focusing on the breastfeeding duration over 6 months, the rate of breastfeeding was higher in controls than in children with ADHD in the same study [18]. In addition, the target of exclusive breastfeeding or non-exclusive breastfeeding might account for different results. For example, the rate of breastfeeding duration over 12 months did not have any significant difference between children with ADHD and controls in the study by Say et al. [19], who focused on exclusive breastfeeding; however, Stadler et al. [6] suggested that the children with ADHD had significantly lower rate of non-exclusive breastfeeding duration over 12 months than that in controls.

Given above-mentioned limitations and gaps within the research literature, the current meta-analysis aimed to investigate the relationships between breastfeeding and ADHD in children, taking into account of important factors such as the duration and methods (e.g., exclusive breastfeeding or non-exclusive breastfeeding with supplementation) of breastfeeding and other important clinical variables, such as age and gender, as moderating factors.

Methods

The current meta-analysis followed the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [20] (supplemental table 1 and supplement figure 1). This meta-analysis fulfilled the requirement of Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-105-12).

Electronic database search, study selection, and data extraction

Two independent authors (PT Tseng and YW Chen) performed a systematic literature search on September 20th, 2017 considering articles published from database inception using the keywords: "(breastfeeding OR breast milk) AND (attention-deficit-hyperactivity disorder OR ADHD OR attention-deficit disorder OR attention deficit hyperactivity disorder OR hyperkinetic disorder)" or similar keywords on PubMed, Embase, ClinicalKey, ScienceDirect, ProQuest, Cochrane Library, and ClinicalTrials.gov platforms. This search strategy was augmented through a manual search of the reference lists of included articles and relevant reviews on this topic [21–23].

The titles/abstracts of retrieved references were independently screened for study eligibility by two authors (PT Tseng and YW Chen) who subsequently screened full texts and a final list was developed through consensus. Whenever a consensus could not be reached, a third author (PY Lin) provided a final decision regarding study eligibility. The eligibility criteria were (a) observational study, including either prospective or retrospective, reporting the difference of breastfeeding duration or percentage of breastfeeding among children with or without ADHD; (b) clinical trials in human; and (c) studies using diagnosis of ADHD based on certain diagnostic criteria [such as diagnostic and statistical manual of mental disorders (DSM) or international statistical classification of diseases and related health problems (ICD)] or by clinicians' clinical diagnosis. The exclusion criteria included (a) studies not conducted with humans; (b) meeting abstracts; (c) case reports or case series; (d) commentary or review articles; and (e) ADHD was not diagnosed by some certain diagnostic criteria or by clinicians.

Two independent authors extracted data using a predetermined database. Variables of interest included: breastfeeding duration (in units of month); percentage of breastfeeding; age; gender distribution; maternal and paternal age of birth; Conners' Parent Rating Scale (CPRS) [24] scores; and Conners' Teacher Rating Form (CTRF) scores [25]; maternal and paternal cognitive function; children's cognitive function (in forms of IQ); maternal and paternal educational levels; maternal and paternal occupational status; maternal and paternal tobacco smoking and alcohol consumption; preterm birth (%); low birth body weight (%); different ethnicity (including African, Caucasian, Asian, and Hispanic); first-born child (%); maternal and paternal history of ADHD; and study follow-up duration.

If the outcome data were not available in potentially eligible studies, we contacted corresponding authors on at least two different occasions via email to request the original data.

Methodology appraisal

We used the modified Newcastle–Ottawa scale (modified NOS) to evaluate the quality of the recruited studies, which had been used in previous psychiatric review article [26]. In brief, in this version of modified NOS, it consisted of four parts of evaluation, including selection bias, performance bias, detection bias, and information bias, with variation of total scores from zero (lowest quality) to twenty-one (highest quality).

Primary outcomes

The primary outcomes were the differences of breastfeeding duration (in units of month) in children with ADHD and controls without ADHD. For the current study, breastfeeding refers to a newborn receiving breast milk either as exclusive (i.e., maternal) breastfeeding or in the form of breastfeeding with concurrent food supplementation. We examined both conditions; namely 'exclusive breastfeeding' or non-exclusive breastfeeding, that is breastfeeding with food supplementation' separately. Furthermore, although the effect sizes (ESs) would be more intuitive by presentation of continuous items, we also arrange meta-analysis in aspect of categorical data (i.e., rate of breastfeeding duration in children with/without ADHD) to expand our findings from the extracted data.

Secondary outcome

We used odds [in calculation of odds ratio (OR)] of receiving breastfeeding in children diagnosed with/without ADHD as the secondary outcome. Furthermore, to clarify the effect of breastfeeding duration on ADHD, we subdivided the recruited studies into subgroup meta-analysis based on the different breastfeeding duration (i.e., under 3, 3–6, 6–12 months, and over 12 months) to compare the rate of different breastfeeding duration in children with ADHD and controls without ADHD. To adjust for the potential confounding clinical variables, we also arranged meta-analysis of the adjusted odds ratio (adjusted OR) provided by the recruited studies, if available, about the association between non-breastfeeding and ADHD.

Meta-analytic method

Due to the anticipated heterogeneity among included studies, a random-effects model was employed [27]. In brief, the random-effects model incorporates a between-study variance in the calculations [28]. For the ESs of differences of duration of breastfeeding was set as Hedges' g and the difference in means with the corresponding 95% confidence intervals (CIs). The ORs with the corresponding 95% CIs of the difference in rate of breastfeeding duration in children with/without ADHD were the set out as the ESs of these meta-analyses of secondary outcome. For all analyses, a two-tailed p value < 0.05 was used to indicate statistical significance. All calculations were conducted with the Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ).

Subgroup meta-analysis, heterogeneity, meta-regression, publication bias, and sensitivity test

We explored whether the results differed according to those who had exclusive versus non-exclusive breastfeeding. Exclusive breastfeeding was defined as an infant receiving breastfeeding without any other supplementary food. Non-exclusive breastfeeding was defined as an infant receiving both breastfeeding and food supplementation. We performed the meta-analytic procedure when at least two datasets available. Heterogeneity was assessed by calculating the Cochrane Q test and corresponding p values [29]. The I^2 statistic indicated the proportion of heterogeneity among the recruited studies [30]. In situation of at least five datasets, we performed meta-regression analyses. The influence of pre-defined potential moderators with unrestricted maximum likelihood random-effects were included in meta-regression analyses. Specifically, we considered age; gender distribution; mean duration of breastfeeding; maternal and paternal age of birth; the CPRS [24]; the CTRF [25]; maternal and paternal cognitive function; children cognitive function; maternal and paternal educational levels; maternal and paternal occupational levels; maternal and paternal tobacco smoking and alcohol consumption; preterm birth; low birth body weight; different ethnicity (including African, Caucasian, Asian, and Hispanic); first-born child; maternal and paternal history of ADHD; and study follow-up duration. Publication bias was investigated via inspection of funnel plots [31] and Egger's regression analysis [32]. If we found evidence of publication bias, we conducted Duval and Tweedie's trim and fill test [33]. Finally, in a sensitivity analyses we removed one study to verify whether a single study could be biasing the summary effect size estimates. In brief, we removed one study at a time and re-analyzed the result of meta-analysis to see if there was any change in the results of meta-analysis. If the results of meta-analysis changed, then, this study might be the outlier or had larger sample sizes [34].

Results

Included studies

A flowchart of study selection for this systematic review and meta-analysis is provided in Fig. 1. Briefly, fifty-five hundred and sixty-nine non-duplicated references were identified. Of those, fifty-five hundred and thirty-eight were excluded after title/abstract screening, and 31 full texts were reviewed. Finally, eleven studies met eligibility criteria for the current meta-analysis [6, 13–19, 35–37]. All of the ADHD diagnosis were made according to diagnostic criteria, such as DSM system or ICD system [6, 14–19, 35–37], or by clinician's record [13]. The reasons for exclusion of articles selected for full-text review are provided in supplementary table 2.

Across the included studies, four provided differences of breastfeeding duration in children with ADHD and controls without ADHD [16, 19, 35, 36] (number of ADHD children = 656, mean age = 9.7, female proportion = 23.5%; number of control children = 369, mean age = 9.1, female proportion = 37.5%); seven studies provided comparison of non-exclusive breastfeeding rate in children with ADHD and controls without ADHD [6, 13, 15–18, 37] (number of ADHD children = 2672, mean age = 10.9, female proportion = 20.2%; number of control children = 77,234, mean age = 11.3, female proportion = 48.6%); four studies provided comparison of exclusive breastfeeding rate in children with ADHD and controls without ADHD [14, 15, 17, 19] (number of ADHD children = 2871, mean age = 10.9, female proportion = 20.2%; number of control children = 89,665, mean age = 11.3, female proportion = 49.1%) (Table 1). Only two of them were prospective cohort study [15, 37]; the other nine studies were retrospective study [6, 13, 14, 16–19, 35, 36]. Among the recruited eleven studies, although we identified the study by Schmitt, we could not fit it into any part of meta-analysis in different breastfeeding duration (i.e., under 3, 3–6,

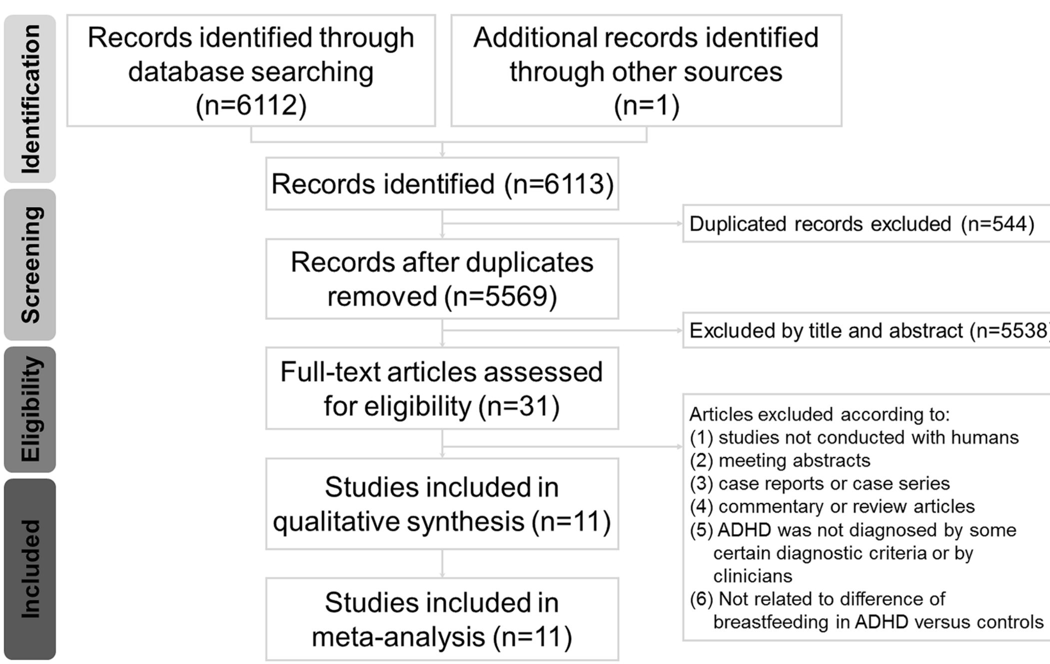


Fig. 1 Flowchart of the study selection for the current meta-analysis

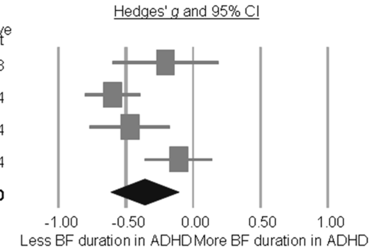
Table 1 Summary of the included studies in current meta-analysis

Study	Criteria of ADHD	Groups	Numbers	Age	Female (%)	Newcastle–Ottawa scale					Country
						Selection	Performance	Detection	Information	Total	
Lemcke, S. (2016)	ICD-10	ADHD Control	2034 76,286	11.3	48.2	3	6	5	5	19	Denmark
Say, G.N. (2016)	DSM-IV	ADHD Control	100 80	8.6	21.4	1	3	5	3	12	Turkey
Stadler, D.D. (2016)	DSM-5	ADHD Control	291 183	8.8	36.1	2	4	5	5	16	USA
Turkoglu, S. (2015)	DSM-IV	ADHD Control	300 75	10.2	26.4	2	4	5	5	16	Turkey
van Dyk, L. (2015)	DSM-IV	ADHD Control	50 50	8.8	20	3	5	5	4	17	South Africa
Field, S.S. (2014) male	DSM-IV	ADHD Control	64 320	n/a	0.0	2	5	5	4	16	USA
Field, S.S. (2014) female	DSM-IV	ADHD Control	17 152	n/a	100.0	2	5	5	4	16	USA
Ptacek, R. (2014)	DSM-IV	ADHD Control	100 100	n/a	0.0	2	5	5	4	16	Czech
Sabuncuoglu, O. (2014)	DSM-IV	ADHD Control	200 175	n/a	37.1	3	5	5	5	18	Turkey
Mimouni-Bloch, A. (2013)	Clinician diagnosis	ADHD Control	56 103	10.5	41.7	3	6	5	5	19	Israel
Schmitt, J. (2012)	ICD-10	ADHD Control	660 12,828	11.2	50.0	3	5	5	5	18	Germany
Kadziela-Olech, H. (2005)	ICD-10	ADHD Control	60 40	7.4	15.0	2	5	5	5	17	Poland

ADHD attention-deficit/hyperactivity disorder, *DSM-5* diagnostic and statistical manual of mental disorders, fifth edition, *DSM-IV* diagnostic and statistical manual of mental disorders, fourth edition, *ICD-10* international statistical classification of diseases and related health problems 10th revision, *n/a* not available

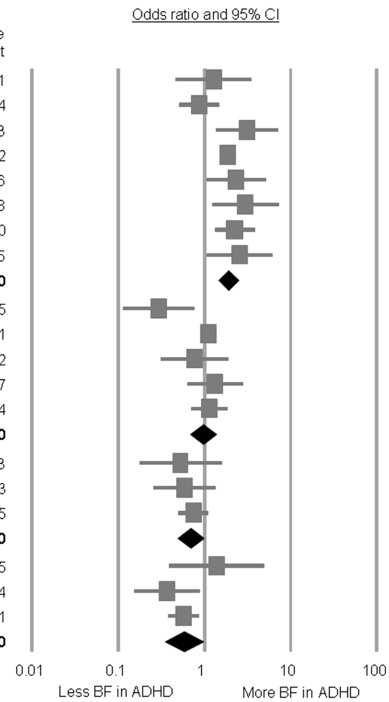
A

Study name	Study design	Exclusive or not	Hedges' g	Lower limit	Upper limit	p-Value	Relative weight
Kadziela-Olech, H. (2005)	Retrospective	Alternative	-0.206	-0.604	0.192	0.311	19.28
Sabuncuoglu, O. (2014)	Retrospective	Exclusive	-0.601	-0.808	-0.394	0.000	29.54
Say, G.N. (2015)	Retrospective	Exclusive	-0.471	-0.772	-0.171	0.002	24.24
Turkoglu, S. (2015)	Retrospective	Alternative	-0.108	-0.360	0.145	0.404	26.94
BF period overall			**-0.360**	**-0.614**	**-0.107**	**0.005**	**100.00**



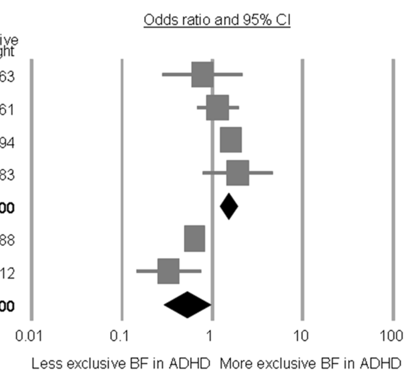
B

BF duration	Study name	Study design	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
0-3	Field, S.S. (2014) (ADHD) female	Retrospective	1.286	0.465	3.555	0.628	5.81
0-3	Field, S.S. (2014) (ADHD) male	Retrospective	0.871	0.509	1.491	0.614	14.64
0-3	Kadziela-Olech, H. (2005)	Retrospective	3.115	1.346	7.212	0.008	7.93
0-3	Lemcke, S. (2016)	Prospective	1.886	1.709	2.081	0.000	33.92
0-3	Mimouni-Bloch, A. (2013)	Retrospective	2.349	1.057	5.218	0.036	8.56
0-3	Ptacek, R. (2014)	Retrospective	2.988	1.223	7.301	0.016	7.18
0-3	Stadler, D.D. (2016)	Retrospective	2.252	1.310	3.871	0.003	14.50
0-3	van Dyk, L. (2015)	Prospective	2.567	1.072	6.150	0.034	7.45
0-3	**0 to 3 months overall**		**1.895**	**1.450**	**2.478**	**0.000**	**100.00**
3-6	Kadziela-Olech, H. (2005)	Retrospective	0.294	0.113	0.764	0.012	10.15
3-6	Lemcke, S. (2016)	Prospective	1.117	0.976	1.278	0.108	40.81
3-6	Mimouni-Bloch, A. (2013)	Retrospective	0.767	0.309	1.904	0.567	10.92
3-6	Ptacek, R. (2014)	Retrospective	1.329	0.633	2.792	0.452	14.57
3-6	Stadler, D.D. (2016)	Retrospective	1.143	0.703	1.856	0.590	23.54
3-6	**3 to 6 months overall**		**0.965**	**0.682**	**1.366**	**0.842**	**100.00**
6-12	Kadziela-Olech, H. (2005)	Retrospective	0.528	0.175	1.595	0.258	9.93
6-12	Mimouni-Bloch, A. (2013)	Retrospective	0.587	0.252	1.364	0.216	17.03
6-12	Stadler, D.D. (2016)	Retrospective	0.748	0.498	1.125	0.163	73.05
6-12	**6 to 12 months overall**		**0.694**	**0.490**	**0.982**	**0.039**	**100.00**
> 12	Kadziela-Olech, H. (2005)	Retrospective	1.385	0.388	4.946	0.616	14.05
> 12	Mimouni-Bloch, A. (2013)	Retrospective	0.367	0.151	0.890	0.027	25.14
> 12	Stadler, D.D. (2016)	Retrospective	0.572	0.380	0.864	0.008	60.81
> 12	**Over 12 months overall**		**0.579**	**0.346**	**0.970**	**0.038**	**100.00**



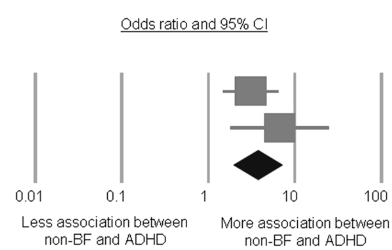
C

BF duration	Study name	Study design	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
0-3	Field, S.S. (2014) (ADHD) female	Retrospective	0.778	0.281	2.150	0.628	4.63
0-3	Field, S.S. (2014) (ADHD) male	Retrospective	1.148	0.671	1.965	0.614	14.61
0-3	Lemcke, S. (2016)	Prospective	1.623	1.465	1.799	0.000	74.94
0-3	Say, G.N. (2015)	Retrospective	1.910	0.777	4.694	0.159	5.83
0-3	**Under 3 months overall**		**1.506**	**1.203**	**1.885**	**0.000**	**100.00**
> 3	Lemcke, S. (2016)	Prospective	0.638	0.581	0.700	0.000	69.88
> 3	Say, G.N. (2015)	Retrospective	0.329	0.144	0.749	0.008	30.12
> 3	**Over 3 months overall**		**0.522**	**0.288**	**0.948**	**0.033**	**100.00**



D

Study name	Study design	Exclusive or not	Odds ratio	Lower limit	Upper limit	p-Value
Mimouni-Bloch, A. (2013)	Retrospective	Alternative	3.080	1.460	6.499	0.003
van Dyk, L. (2015)	Prospective	Alternative	6.650	1.771	24.972	0.005
Adjusted OR overall			**3.709**	**1.936**	**7.107**	**0.000**



◂**Fig. 2** **a** Forest plot of meta-analysis of difference of breastfeeding duration in ADHD children and controls; **b** forest plot of meta-analysis of rate of different non-exclusive breastfeeding duration in ADHD children and controls; **c** forest plot of meta-analysis of rate of different exclusive breastfeeding duration in ADHD children and controls; **d** forest plot of meta-analysis of adjusted odds ratio of association between non-breastfeeding and ADHD. **a** indicated the breastfeeding duration is significantly shorter in ADHD children than in controls (Hedges' $g = -0.360$, 95% CIs $= -0.614$ to -0.107, $p = 0.005$); **b** suggested that the rate of non-exclusive breastfeeding is significantly higher in breastfeeding duration under 3 months (OR = 1.895, 95% CIs = 1.450 to 2.478, $p < 0.001$) but lower in non-exclusive breastfeeding duration between 6 and 12 months (OR = 0.694, 95% CIs = 0.490 to 0.982, $p = 0.039$) or over 12 months (OR = 0.579, 95% CIs = 0.346 to 0.970, $p = 0.038$) in ADHD children than those in controls; **c** revealed that the rate of exclusive breastfeeding is significantly higher in breastfeeding duration under 3 months (OR = 1.506, 95% CIs = 1.203 to 1.885, $p < 0.001$) but lower in exclusive breastfeeding duration over 3 months (OR = 0.522, 95% CIs = 0.288 to 0.948, $p = 0.033$) in ADHD children than those in controls; **d** found that result of meta-analysis of pooled adjusted OR provided significantly association between non-breastfeeding and ADHD (adjusted OR = 3.709, 95% CIs = 1.936 to 7.107, $p < 0.001$). *ADHD* attention-deficit/hyperactivity disorder, *BF* breastfeeding, *CI* confidence interval, *MA* meta-analysis, *n/a* not applicable, *OR* odds ratio

6–12 months, or over 12 months) due to lack of detailed information available [14].

Quality appraisal of the recruited studies

Among these eleven recruited studies, the mean modified NOS scores were 16.7 with standard deviation (SD) 2.0 (Table 1).

Is breastfeeding duration shorter in children with ADHD?

Among the four studies providing the difference of breastfeeding duration in children with ADHD and controls without ADHD [16, 19, 35, 36], the results of the meta-analysis indicated that the breastfeeding duration was shorter in children with ADHD than that in controls without ADHD (Hedges' $g = -0.36$, 95% CIs $= -0.61$ to -0.11, $p = 0.005$) (Fig. 2a) with significant heterogeneity (Q value = 9.88, $df = 3$, $p = 0.020$, $I^2 = 69.64\%$, tau = 0.213) but not publication bias via inspection of funnel plot or Egger's regression (t value = 0.79, $df = 2$, $p = 0.515$). Furthermore, the mean difference of breastfeeding duration between ADHD children and controls were − 2.44 months (difference in means: − 2.44 months, 95% CIs = − 3.17 to − 1.71, $p < 0.001$) without significant heterogeneity (Q value = 2.59, $df = 3$, $p = 0.460$, $I^2 < 0.01\%$, tau < 0.01) or publication bias via inspection of funnel plot or Egger's regression (t value = 0.48, $df = 2$, $p = 0.677$).

The sensitivity test with one study removal test revealed that the significance would change into insignificant finding after removing the data by Say et al. (Hedges' $g = -0.32$, 95% CIs = − 0.67 to 0.03, $p = 0.072$), which might be due to the smaller sample sizes after removal of the data by Say et al. [19].

The meta-regression procedure and subgroup meta-analysis could not be performed due to the limited datasets available.

Is there any different rate of non-exclusive breastfeeding duration in children with ADHD?

We separated the recruited studies with non-exclusive breastfeeding duration of under 3 months [6, 13, 15–18, 37], 3–6 months [6, 13, 15, 16, 18], 6–12 months [6, 13, 16], and over 12 months [6, 13, 16]. The distribution of different non-exclusive breastfeeding duration had transitional pattern along with the breastfeeding duration.

The rate of non-exclusive breastfeeding duration under 3 months was significantly higher in children diagnosed with ADHD than those without ADHD (7 studies with 8 datasets, OR = 1.90, 95% CIs = 1.45–2.48, $p < 0.001$) [6, 13, 15–18, 37] (Fig. 2b, Table 2) without significant heterogeneity (Q value = 12.05, $df = 7$, $I^2 = 41.91\%$, $p = 0.099$, tau = 0.229) or evidence of publication bias via inspection of funnel plot or Egger's regression ($t = 0.21$, $df = 6$, $p = 0.844$). The sensitivity test with one study removal test revealed that the significance would not change after removing any one of the recruited studies. Therefore, the significant finding of this part of meta-analysis was not contributed by any single outlier of the recruited studies. The meta-regression suggested that there was no any significant association between the rate of non-exclusive breastfeeding duration under 3 months and the clinical variables, including mean age ($p = 0.153$), female proportion ($p = 0.932$), and proportion of preterm birth ($p = 0.303$). Furthermore, if we focused on the results provided by prospective trials only, the results of meta-analysis still revealed that the rate of non-exclusive breastfeeding duration under 3 months was significantly higher in children diagnosed with ADHD than those without ADHD (2 studies with 2 datasets, OR = 1.89, 95% CIs = 1.72–2.09, $p < 0.001$) [15, 37].

The rate of non-exclusive breastfeeding duration with 3–6 months did not have any significant difference in children diagnosed with ADHD versus controls without ADHD (5 studies with 5 datasets, OR = 0.97, 95% CIs = 0.68–1.37, $p = 0.842$) [6, 13, 15, 16, 18] (Fig. 2b, Table 2) without significant heterogeneity (Q value = 8.24, $df = 4$, $I^2 = 51.44\%$, $p = 0.083$, tau = 0.269) or evidence of publication bias via inspection of funnel plot or Egger's regression ($t = 1.12$, $df = 3$, $p = 0.343$). The sensitivity test with one study removal test revealed that the insignificance would not change after removing any one of the recruited studies. The meta-regression suggested that there was no any significant association

Table 2 Summary of main findings in rate of BF in different BF duration in children with ADHD and controls

BF duration (months)	Odds ratio	95% CI lower limit	95% CI upper limit	*p* value	Dataset numbers	Results
Non-exclusive						
0–3	1.895	1.450	2.478	< 0.001	8	More in ADHD
3–6	0.965	0.682	1.366	0.842	5	No difference
6–12	0.694	0.490	0.982	0.039	3	More in control
> 12	0.579	0.346	0.970	0.038	3	More in control
Exclusive						
0–3	1.506	1.203	1.885	< 0.001	4	More in ADHD
> 3	0.522	0.288	0.948	0.033	2	More in control

ADHD attention-deficit/hyperactivity disorder, *BF* breastfeeding, *CI* confidence interval

between the rate of non-exclusive breastfeeding duration under 3 months and the clinical variables, including female proportion ($p=0.403$). The subgroup meta-analysis would not be performed because there were less than 2 datasets of prospective trial.

The rate of non-exclusive breastfeeding duration with 6–12 months was significantly less in children diagnosed with ADHD than those without ADHD (3 studies with 3 datasets, OR = 0.69, 95% CIs = 0.49–0.98, $p=0.039$) [6, 13, 16] (Fig. 2b, Table 2) without significant heterogeneity (Q value = 0.52, $df=2$, $I^2<0.001\%$, $p=0.772$, tau < 0.001), but significant publication bias via inspection of funnel plot and Egger's regression ($t=15.90$, $df=1$, $p=0.040$). Via the Duval and Tweedie's trim and fill test, the adjusted ESs after adding two potential missing values to the right side of mean were OR = 0.75 (95% CIs = 0.55–1.02). The sensitivity test with one study removal test revealed that the significance would change into insignificance after removing any one of the recruited studies, which might be due to the fewer sample sizes included after removal any one the studies. The meta-regression and the subgroup meta-analysis could not be performed due to limited datasets available. Furthermore, the subgroup meta-analysis could not be performed because there were less than 2 datasets of prospective trial.

The rate of non-exclusive breastfeeding duration over 12 months was significantly less in children diagnosed with ADHD than those without ADHD (3 studies with 3 datasets, OR = 0.58, 95% CIs = 0.35–0.97, $p=0.038$) [6, 13, 16] (Fig. 2b, Table 2) without significant heterogeneity (Q value = 2.82, $df=2$, $I^2=29.02\%$, $p=0.244$, tau = 0.264) or evidence of publication bias via inspection of funnel plot or Egger's regression ($t=0.33$, $df=1$, $p=0.799$). The sensitivity test with one study removal test revealed that the significance would change into insignificance after removing the data by Stadler et al. (OR = 0.66, 95% CIs = 0.18–2.39, $p=0.524$) [6] or removing the data by Mimouni-Bloch et al. (OR = 0.72, 95% CIs = 0.34–1.53, $p=0.393$) [13]. The meta-regression, subgroup and sensitivity meta-analysis could not be performed due to limited datasets available.

Is there any different rate of exclusive breastfeeding duration in children with ADHD?

At this part of meta-analysis, because the limited datasets available, we could only separate the recruited studies with exclusive breastfeeding duration into subgroup of under 3 months [15, 17, 19] and those of over 3 months [15, 19].

The rate of exclusive breastfeeding duration under 3 months was higher in children diagnosed with ADHD than those without ADHD (3 studies with 4 datasets, OR = 1.51, 95% CIs = 1.20–1.89, $p<0.001$) [15, 17, 19] (Fig. 2c, Table 2) without significant heterogeneity (Q value = 3.62, $df=3$, $I^2=17.07\%$, $p=0.306$, tau = 0.122) or evidence of publication bias via inspection of funnel plot or Egger's regression ($t=1.29$, $df=2$, $p=0.327$). The sensitivity test with one study removal test revealed that the significance would change into insignificance after removing the datasets by Lemcke et al. (OR = 1.20, 95% CIs = 0.79–1.83, $p=0.394$) [15] or the datasets by Say et al. (OR = 1.38, 95% CIs = 0.98–1.95, $p=0.064$) [19]. The meta-regression and the subgroup meta-analysis could not be performed due to limited datasets available. Furthermore, the subgroup meta-analysis could not be performed because there were less than 2 datasets of prospective studies.

The rate of exclusive breastfeeding duration over 3 months was less in children diagnosed with ADHD than those without ADHD (2 studies with 2 datasets, OR = 0.52, 95% CIs = 0.29–0.95, $p=0.033$) [15, 19] (Fig. 2c, Table 2) without significant heterogeneity (Q value = 2.45, $df=1$, $I^2=59.21\%$, $p=0.117$, tau = 0.361). The sensitivity test with one study removal test revealed that the significance did not change after removing any one of the recruited studies. The meta-regression and the subgroup meta-analysis could not be performed due to limited datasets available. Furthermore, the subgroup meta-analysis could not be performed because there were less than 2 datasets of prospective trial.

Is there still any association between ADHD and non-breastfeeding after adjusted by the potential confounding factors?

There were only two studies that provided the adjusted OR about the association between ADHD and non-breastfeeding, either in the exclusive or non-exclusive forms [13, 37]. The result of meta-analysis found that the pooled adjusted OR favor significant association between non-breastfeeding and ADHD (adjusted OR = 3.71, 95% CI = 1.94–7.11, $p < 0.001$) (Fig. 2d) without significant heterogeneity (Q value = 0.97, $df = 1$, $I^2 < 0.001\%$, $p = 0.321$, tau < 0.001). The sensitivity test with one study removal test revealed that the significance would not change after removing any one of the recruited studies. The meta-regression and subgroup meta-analysis could not be performed due to limited datasets available. Furthermore, the subgroup meta-analysis could not be performed because there were less than 2 datasets of prospective trial.

Discussion

The current meta-analysis summarizes the relationships between breastfeeding and ADHD in children, suggesting that the mean breastfeeding duration is less in children with ADHD than that in controls without ADHD with a mean difference of 2.44 months. Furthermore, the ADHD children stopped breastfeeding earlier than controls (higher rate of less than 3 months breastfeeding in ADHD (OR = 1.90) and lower rate of between 6 and 12 months breastfeeding (OR = 0.69) or more than 12 months breastfeeding (OR = 0.58) in ADHD than those in controls). To be clear, the odds of breastfeeding under 3 months related to breastfeeding over 3 months in ADHD children is 1.895 times as that in controls. Therefore, those children with breastfeeding duration under 3 months had higher risk of ADHD to that with breastfeeding duration over 3 months. In addition, this relationship remained significant when we restricted our analysis to either exclusive breastfeeding or non-exclusive breastfeeding with other complementary foods. Finally, the pooled adjusted odds ratio from the recruited studies also provided significantly higher association between non-breastfeeding and ADHD (adjusted OR = 3.71).

The relationships between non-breastfeeding and ADHD could potentially be explained by the fact that children with ADHD may have been overtly hyperactive or inattentive during early infancy and, therefore, could not cooperate with the breastfeeding process over a sustained period of time [38]. This may have led to a scenario where the duration of breastfeeding was already directly affected by the presentation of early ADHD traits. In addition to the difficulties during breastfeeding children with ADHD, the higher rates of psychopathology were also found in ADHD children's mothers according to the reports from other studies, such as maternal childhood ADHD, anxiety disorder, and depression [39], which would also decrease the motivation providing breastfeeding to their children [40].

Previously, one sibling controlled study reported the onset of ADHD might be modified by some interventions, such as the promotion of breastfeeding [13]. In that study, the authors compared the presence of breastfeeding in children diagnosed with ADHD with their sibling controls across different ages. The authors found that breastfeeding rates were significantly higher in sibling controls than children with ADHD across all different ages. Consistent with our meta-analysis, the presence of ADHD was significantly lower in children in receipt of breastfeeding than those without. However, the establishment of continuous breastfeeding procedure may be complicated and disturbed by severity of ADHD symptoms when the child has at least severe ADHD. This possible scenario may complicate the interpretation of findings in studies investigating association between breastfeeding and ADHD. Furthermore, there were other potential confounding factors not assessed in our meta-analysis, such as the potential maternal ADHD diagnosis among those children with ADHD. In previous reports, the prevalence rate of diagnosis of ADHD among the mothers of ADHD children achieve 16.7–25.2% [39, 41]. Furthermore, in the report by Babinski et al. [41], the authors found mothers with a diagnosis of ADHD had more problems in parenting and psychopathology than those in mother without diagnosis of ADHD. All of these problems may have influenced the breastfeeding process.

There have been some additional suggestions that breastfeeding may ameliorate the severity of ADHD. Groen-Blokhuis and colleagues found that the severity of ADHD, attention problems and hyperactivity, was significantly lower in children who were breastfed than those without breastfeeding [42]. This finding has been supported by another report, that found less internalizing and overall behavioral problems in children with breastfeeding than those without breastfeeding [43]. All these phenomena indicate that the procedure of breastfeeding might help in the modification of the presentation of ADHD, or at least an environmentally potential risk factor. The precise pathophysiological processes underlying a potential link between ADHD and breastfeeding, however, have not been fully elucidated [22].

Breastfeeding may also improve offspring attention through a shifting effect on cytokine patterns. Specifically, children with adequate breastfeeding have significantly lower blood interferon-gamma levels than those with formula-feeding [44]. Higher interferon-gamma levels, longer response time and poorer attention levels have all been reported in children with ADHD [45]. Various other immune functions in relation to signaling and inflammatory mechanisms could also be relevant. Several other factors may also account for the relationship between risk of childhood ADHD and breastfeeding practices. These include a possible role for the polyunsaturated fatty acids (PUFAs) such as omega-3 and omega-6 fatty acids abundant in early breast milk or the influence of breast milk on the developing infant gut microbiome in relation to risk of ADHD.

It is potentially troublesome for some women, such as those who go back to work early, to provide exclusive breastfeeding [46–48]. Therefore, we conducted further subgroup meta-analysis considering those who did and did not receive exclusive breastfeeding. We found both the results of meta-analysis in exclusive breastfeeding and non-exclusive breastfeeding plus supplementary feeding provided similar results. This reinforces the message that for those women who may struggle with breastfeeding exclusively, supplementary feeding also appears to be associated with a lower risk of ADHD.

This study has the following limitations. First, our collected data is observational studies and although we detected some quite consistent relationships, causality cannot be inferred at the current time. Second, most recruited articles were retrospective studies. Although we tried to arrange subgroup meta-analysis of prospective trials only ($n=2$), the lack of data precludes any definitive conclusions. Third, the total numbers of eligible studies were relatively small, potentially resulting in a risk for possible type I and type II errors. Fourth, although we tried to conduct subgroup meta-analysis, the relatively small study numbers in some of these groups deserve a more careful interpretation of findings. Fifth, some potentially eligible studies (e.g., Schmitt et al. [14]) could not be included as the papers did not have sufficient data and the authors did not respond to our email requests. Six, we encountered some heterogeneity and publication bias among some parts of the meta-analyses, which would result in implication to the results. Finally, we could only arrange meta-analysis of pooled adjusted OR based on few studies because of limited data available. To overcome this, we tried to evaluate the relationship between those confounding factors and the ESs via meta-regression and subgroup analyses. We also attempted to contact study authors for additional data, but could not perform comprehensive meta-regression of all potential clinical variables due to limited data.

Conclusion

The results of the current study suggest that breastfeeding duration was shorter in children with ADHD than in controls. Furthermore, those children with shorter breastfeeding duration appear to have a higher risk of ADHD. Both exclusive and non-exclusive breastfeeding with supplements seemed to confer a similar result. Future longitudinal work is required to disentangle the various relationships observed and attempt to understand potential mechanistic pathways underlying this important association.

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Compliance with ethical standards

Conflict of interest The authors state that there are no any competing interests in the current literature.

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